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(54) Title: PHARMACEUTICAL FORMULATIONS FOR TREATING POSTMENOPAUSAL AND PERIMENOPAUSAL WOMEN, AND THEIR USE

(57) Abstract: Disclosed are pharmaceutical formulations containing various combinations of an estrogen, a progestin, an androgen, a selective estrogen receptor modulator, a selective androgen receptor modulator, and/or a selective progestin receptor modulator for use in treating postmenopausal or perimenopausal women. Also disclosed are methods for treating such women with the pharmaceutical formulations of the invention.

# PHARMACEUTICAL FORMULATIONS FOR TREATING POSTMENOPAUSAL AND PERIMENOPAUSAL WOMEN, AND THEIR USE

## Field of the Invention

The invention relates to pharmaceutical formulations and methods for treating postmenopausal and perimenopausal women.

## Background of the Invention

Postmenopausal women, including young women who suffer from ovarian dysfunction due to surgical, radiation, or chemotherapy induced ablation, for example, typically exhibit particular physiological signs associated with impairment of ovarian function. For example, such women typically experience a loss of calcium from the skeleton, leading to a reduction in bone density or in the quantity of bone. In addition, such women may have increased cholesterol levels, leading to atherosclerosis. Other symptoms include depression, headaches, and nausea. Perimenopausal women experience a change in the intermenstrual cycle interval, along with other associated symptoms of estrogen deficiency, such as vasomotor flushes, vaginal dryness, or worsening premenstrual syndromes.

## Summary of the Invention

This invention provides pharmaceutical formulations and methods for treating perimenopausal or postmenopausal women, including women of all ages having premature ovarian failure (e.g., young women who have had an ablation of ovarian function due to surgery, radiation, or chemotherapy). An exemplary pharmaceutical formulation of the invention includes (i) an androgen or a selective androgen receptor modulator (SARM), (ii) an estrogen or a selective estrogen receptor modulator (SERM), and (iii) a progestin or a selective progestin receptor modulator (SPRM) in a pharmaceutically acceptable carrier. The pharmaceutical formulation can be administered to a postmenopausal woman or a perimenopausal woman in a method of treatment.

In a related aspect, the invention features a pharmaceutical formulation that includes (i) a SERM and (ii) an androgen or a SARM in a pharmaceutically acceptable carrier. Optionally, this pharmaceutical formulation also includes (iii) a progestin or a SPRM. Pharmaceutical formulations containing a therapeutically effective amount of a SERM and an androgen or SARM, and optionally a progestin or SPRM, can be used to treat postmenopausal women and perimenopausal women.

Also within the invention is a pharmaceutical formulation that includes (i) a SERM and (ii) an estrogen, and optionally (iii) a progestin or SPRM. Such a pharmaceutical formulation, containing a therapeutically effective amount of the SERM and estrogen, and optionally progestin, can be used in

methods of treating postmenopausal and perimenopausal women.

In another variation of the above-described pharmaceutical formulations, the invention includes a pharmaceutical formulation containing (i) a SERM, (ii) an estrogen, and (ii) an androgen or SARM, and optionally (iv) a progestin or SPRM. Such a pharmaceutical formulation containing the SERM, estrogen, androgen, and optionally progestin, in a therapeutically effective amount can be used in methods of treating postmenopausal and perimenopausal women.

A variety of estrogens, progestins, androgens, SERMs, SARMs, and SPRMs can be used in the invention. Examples of suitable estrogens include conjugated estrogens, esterified estrogens, estradiol valerate, estradiol benzoate, 17-β estradiol, estradiol cypionate, estrone, piperazine estrone sulfate, estriol, ethyl estradiol, polyestradiol phosphate, estrone potassium sulfate, benzestrol, chlorotrianisene, methallenestril, dienestrol, diethylstilbestrol diphosphate, mestranol, diethylstilbestrol (DES), quinestranol, and phytoestrogens. Animal-derived estrogens (e.g., equine estrogens) and their metabolic derivatives also are suitable for use in the invention, and are commercially available.

Examples of suitable progestins include progesterone, 17-hydroxy progesterone derivatives, 19-nor testosterone derivatives, norethindrone, norethindrone acetate, norethynodrel, norgestrel, norgestimate, ethynodiol diacetate, allylestrenol,

lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone levo-norgestrel, dl-norgestrel, cyproterone acetate, gestodene, desogestrol, phytoprogestins, dydrogesterone, ethynodiol diacetate, medroxyprogesterone acetate, phytoprogestins, and megestrol acetate. Animal-derived progestins (e.g., equine progestins) and their metabolic derivatives also are suitable for use in the invention.

Examples of suitable androgens include testosterone, methyltestosterone, fluoxymesterone, testosterone cypionate, testosterone enanthate, testosterone propionate, oxymetholone, ethylestrenol, oxandrolone, nandrolone phenpropionate, nandrolone decanoate, stanozolol, dromostanolone propionate, androstenedione, dehydropepiandrosterone, dehydroepiandrosterone sulfate (DHEAS), dihydrotestosterone, and phytoandrogens. Animal-derived androgens (e.g., equine androgens) and their metabolic derivatives also are suitable for use in the invention.

Examples of suitable SERMs include tamoxifen, raloxifene, clomiphene, droloxifene, idoxifene, toremifene, tibolone, ICI 182,780, ICI 164,384, diethylstilbesterol, genistein, nafoxidine, moxestrol, 19-nor-progesterone derivatives, and 19-nor-testosterone derivatives.

Examples of suitable SARMs include cyproterone acetate, hydroxyflutamide, bicalutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g]quinolinone derivatives, 1,2-

dihydropyridono[5,6-g]quinoline derivatives, and piperidino[3,2-g]quinolinone derivatives.

Examples of suitable SPRMs include RU486, CDB2914, 19-nor-progesterone derivatives, 19-nor-testosterone derivatives, 6-aryl-1,2-dihydro-2,2,4-trimethylquinoline derivatives, 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]quinoline derivatives, 5-alkyl 1,2-dihydrochomeno[3,4-f]quinoline derivatives, and 6-thiophenehydroquinoline derivatives.

In various preferred embodiments, the pharmaceutical formulations described herein are contained within a transdermal patch or an intravaginal ring for delivery of the pharmaceutical formulation to the woman. Other transdermal routes (e.g., through the use of topically applied creams, ointments, and the like) and other intravaginal routes (e.g., through the use of suppositories, creams, and the like) also can be used in the invention. Alternatively, the pharmaceutical formulations can be prepared for administration via routes such as oral, intranasal, buccal, ocular, aural, injectable depot, subcutaneous, intraperitoneal, intrauterine, sublingual, or intramuscular routes of administration. If desired, more than one route of administration can be used to deliver the estrogen, androgen, progestin, SERM, SARM, and/or SPRM to the woman (e.g., oral and transdermal routes). If desired, multiple estrogens, androgens, progestins, SERMs, SARMs, and/or SPRMs can be used to prepare the pharmaceutical formulation or to treat the woman in lieu of a single estrogen, androgen, progestin,

SERM, SARM, and/or SPRM.

A "postmenopausal" woman is one who in the absence of hormone replacement therapy or other medication would experience at least 12 months of amenorrhea or levels of serum follicle-stimulating hormone greater than 30 mIU/ml.

A "perimenopausal" woman is one who in the absence of hormone replacement therapy or other medication would experience a change in her intermenstrual cycle interval and have associated symptoms of estrogen deficiency, such as vasomotor flushes, vaginal dryness, and worsening premenstrual syndrome. Also included are women who in the absence of hormone replacement therapy or other medication would experience less than 12 months of amenorrhea.

An "androgen" is a natural or synthetic agent that stimulates activity of the accessory male sex organs and/or muscle development and/or encourages development of male sex characteristics. Examples of suitable androgens include, without limitation, testosterone, methyltestosterone, fluoxymesterone, testosterone cypionate, testosterone enanthate, testosterone propionate, oxymetholone, ethylestrenol, oxandrolone, nandrolone phenpropionate, nandrolone decanoate, testosterone buccilate, stanozolol, dromostanolone propionate, androstenedione, dehydropepiandrosterone, DHEAS, dihydrotestosterone, phytoandrogens, animal-derived androgens, and metabolic derivatives of animal-derived androgens.

A "progestin" is an agent, natural or

synthetic, that effects some or all of the biological changes produced by progesterone, which is a hormone of the corpus luteum. For example, a progestin can induce secretory changes in the endometrium. Examples of progestins include, without limitation, progesterone, 17-hydroxy progesterone derivatives, 19-nor-testosterone derivatives, 19-nor-progesterone derivatives norethindrone, norethindrone acetate, norethynodrel, norgestrel, norgestimate, ethynodiol diacetate, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone levo-norgestrel, dl-norgestrel, cyproterone acetate, gestodene, desogestrol, dydrogesterone, ethynodiol diacetate, medroxyprogesterone acetate, megestrol acetate, phytoprogestins, animal-derived progestins, and metabolic derivatives of animal-derived progestins.

An "estrogen" is an agent, natural or synthetic, that exerts biological effects characteristic of estrogenic hormones such as estradiol. As used herein, the term "estrogen" also encompasses "conjugated estrogens," which are an amorphous preparation of naturally occurring, water-soluble, conjugated forms of mixed estrogens that typically are obtained from the urine of pregnant mares (e.g., sodium estrone sulfate). Also included are "esterified estrogens," which are a mixture of the sodium salts of sulfate esters or glucanoride of sulfate conjugates of estrogenic substances. Examples of suitable estrogens include, without limitation, estradiol valerate, estradiol benzoate,

17-β estradiol, estradiol cypionate, estrone, piperazine estrone sulfate, estriol, ethyl estradiol, polyestradiol phosphate, estrone potassium sulfate, benzestrol, chlorotrianisene, methallenestril, dienestrol, diethylstilbestrol diphosphate, mestranol, DES, quinestranol, phytoestrogens, animal-derived estrogens (e.g., equine estrogens), and metabolic derivatives of animal-derived estrogens.

A "selective estrogen receptor modulator" (SERM) is a compound that is an estrogen analog and which exerts tissue-selective effects. Such compounds can function as estrogen antagonists or partial agonists.

A "selective androgen receptor modulator" (SARM) is a compound that is an androgen analog and which exerts tissue-selective effects. Such compounds can function as androgen antagonists or partial agonists.

A "selective progestin receptor modulator" (SPRM) is a compound that is an progesterone analog and which exerts tissue-selective effects. Such compounds can function as progesterone antagonists or partial agonists.

The invention offers several advantages. For example, the hormone replacement methods of the invention can be used to restore normal physiologic levels of all gonadal steroids for optimal management of symptoms. Other features and advantages of the invention will be evident from the following detailed description of the preferred embodiments, and from the claims.

## Description of the Preferred Embodiments

The pharmaceutical formulations and therapeutic methods of the invention are suitable for virtually all postmenopausal and perimenopausal women.

## Preparation of Pharmaceutical Formulations

The pharmaceutical formulations of the invention include a pharmaceutically acceptable carrier and one of the following combinations of active ingredients:

(A) (i) an androgen or SARM, (ii) an estrogen or SERM, and (iii) a progestin or SPRM;

(B) (i) a SERM and (ii) an androgen or SARM, and optionally (iii) a progestin or SPRM;

(C) (i) a SERM and (ii) an estrogen, and optionally (iii) a progestin or SPRM; or

(D) (i) a SERM, (ii) an estrogen, and (iii) an androgen or SAM, and optionally (iv) a progestin or SPRM.

Such formulations typically contain from about 0.1 to 90% by weight (such as 1 to 20% or 1 to 10%) of the active ingredients in a pharmaceutically acceptable carrier.

In a preferred embodiment, the pharmaceutical formulations are prepared for delivery via an intravaginal ring. Intravaginal rings are well known in the art, and such rings can readily be adapted to contain the above-described combinations of active ingredients in a pharmaceutically acceptable carrier. Typically, in preparing a

pharmaceutical formulation for administration via an intravaginal ring, an oil or water is used as the carrier.

Examples of suitable intravaginal rings are disclosed in U.S. Patents No. 4,762,717; 5,130,137; 4,012,496; 3,854,480; 4,391,797; 4,591,496; and 5,330,768, which are incorporated herein by reference. Typical intravaginal rings that can be adapted for use in the invention are made of ethylvinylacetate. Typically, the intravaginal ring includes estrogen or a SERM at a level sufficient to recreate estrogen effects equivalent to those encountered in the early follicular phase of a typical, normal menstrual cycle. The androgen or SARM typically is contained within the ring at a level sufficient to recreate androgen effects equivalent to those encountered in the early follicular phase of a typical, normal menstrual cycle. Typically, the progestin or SPRM is included at a level sufficient to recreate progestin effects equivalent to those encountered in the luteal phase of a typical, normal menstrual cycle. Examples of suitable dosages are described below.

In another preferred embodiment, the pharmaceutical formulations of the invention are contained within a transdermal patch. Numerous transdermal patches are known in the art and can readily be adapted to contain and deliver the pharmaceutical formulations of the invention. Examples of suitable transdermal patches are disclosed in U.S. Patents No. 5,223,261; 3,598,123; 4,460,372; 3,598,122; 4,573,996; and 4,624,665,

which are incorporated herein by reference. Typical transdermal patches have a flexible backing, a drug reservoir layer, a semipermeable membrane, and an adhesive layer coated on the exterior surface of the semipermeable membrane. Theratech patch technology, for example, can be used in the invention. If desired, the patch may contain a skin penetration enhancer (e.g., a fatty acid ester of a fatty acid such as ethyl oleate, glyceryl monolaurate, and/or isopropyl myristate).

In an alternative patch, the pharmaceutical formulation is contained within the adhesive coating, rather than in a distinct drug reservoir layer. Such a patch may contain, for example, a flexible backing (e.g., polyethylene, polypropylene, polyurethane, and the like) and a pressure-sensitive adhesive coating contiguously adhered to one surface of the backing and containing a homogenous mixture of: (*i*) an acrylic polymer containing a hydrophobic monomeric acrylic or methacrylic ester of an alkyl alcohol (containing 4-10 carbons), polyanhydrides, polyvinylacetate, polylactide or polyglycolide mixes; (*ii*) the active ingredients, each in an amount of about 0.2 to 12 percent of the total weight of the adhesive coating; and (iii) a skin penetration enhancer that includes isopropyl myristate and glyceryl monolaurate each in an amount of about 1 to 20 percent of the weight of the adhesive coating. These examples are non-limiting, and other transdermal patches can be used in conjunction with the pharmaceutical formulations of the invention.

Solid formulations for oral administration can contain suitable carriers or excipients, such as corn starch, gelatin, lactose, liposomes, acacia, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, calcium carbonate, sodium chloride, or alginic acid. Disintegrators that can be used include, without limitation, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid. Tablet binders that may be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch, and ethylcellulose. Lubricants that may be used include magnesium stearates, stearic acid, silicone fluid, talc, waxes, oils, and colloidal silica.

Liquid formulations for oral or sublingual administration typically are prepared in water or other aqueous vehicles. The liquid formulations also can include solutions, emulsions, syrups, and elixirs containing, together with the active ingredients, wetting agents, sweeteners, and coloring and flavoring agents. Various liquid and powder formulations can be prepared by conventional methods for inhalation by the woman.

Injectable formulations can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polylactide, polyglycolide, polyols, (glycerol, propylene glycol, liquid polyethylene glycol, and the like). For intravenous injections, the compounds may be

administered by the drip method, whereby a pharmaceutical formulation containing the active ingredients and a pharmaceutically acceptable carrier is infused. Pharmaceutically acceptable carries can include, for example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable carriers. For intramuscular preparations, a sterile formulation containing the active ingredients can be administered in a pharmaceutical carrier such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

A topical semi-solid ointment formulation typically contains a concentration of the active ingredients from about 1 to 20% (e.g., 5 to 10%) in a carrier such as a pharmaceutical cream base. Various formulations for topical use include drops, tinctures, lotions, creams, solutions, and ointments containing the active ingredient and various supports and vehicles.

The pharmaceutical formulations of the invention can be administered to the woman via a variety of combinations of routes of administration. For example, an androgen, estrogen, and progestin can be combined and delivered transdermally (e.g., via a transdermal patch). Alternatively, an estrogen can be administered orally, while the progestin and androgen are administered transdermally. In yet another suitable method, an androgen, estrogen, and progestin are administered orally. Similarly, the androgen, estrogen, and progestin can be administered via an intravaginal ring. These examples are non-limiting, and a

variety of combinations of routes of administration can be used in the invention.

Therapeutic Regimens

Virtually all postmenopausal and perimenopausal women can be treated with the methods of the invention. If desired, such a woman can be identified as being in need of hormone replacement therapy (using standard criteria, as described, for example, by the American College of Physicians Guidelines (incorporated herein by reference)) prior to treatment of the woman with the methods of the invention. A variety of therapeutic regimens are suitable for use in the invention, and practitioners of ordinary skill in the art can readily optimize a particular regimen for a particular woman by monitoring the woman for signs and symptoms of hormone deficiency, and increasing or decreasing the dosage and/or frequency of treatment as desired.

Regardless of the route of administration, the androgen typically is administered at a daily dosage of 0.01 μg to 5 mg/kg of body weight (e.g., 1 μg/kg to 5 mg/kg), the estrogen typically is administered at a dosage of 0.01 μg/kg to 4 mg/kg (e.g., 0.2 μg/kg to 100 μg/kg), and the progestin typically is administered at a dosage of 0.02 mg/kg to 200 mg/kg (e.g., 2 μg/kg to 10 mg/kg). A SARM typically is administered at a daily dosage of 0.01 μg/kg to 100 mg/kg of body weight (e.g., 1 μg/kg to 4 mg/kg), a SERM typically is administered at a dosage of 0.01 μg/kg to 100 μg/kg (e.g., 1 μg/kg to 2 mg/kg), and a SPRM typically is administered at a

dosage of 0.01μg/kg to 100 mg/kg (e.g., 1 μg/kg to 30 mg/kg). The pharmaceutical formulation can be administered in multiple doses per day, if desired, to achieve the total desired daily dose. Typically, the woman will be treated over the course of several months or years, or even life-long to ameliorate the signs and symptoms resulting from natural or induced impairment of ovarian function.

In one example of a suitable method of treatment, the therapeutic regimen entails administering to the woman a pharmaceutical formulation containing each of (i) an androgen or SARM, (ii) an estrogen or SERM, and (iii) a progestin or SPRM at least once daily for 13 to 14 days, followed by administering each of (i) an estrogen or SERM and (ii) an androgen or SARM at least once daily for 13 to 14 days. The dosages listed above are suitable.

In another method, the woman is treated with a pharmaceutical formulation containing each of (i) a SERM, (ii) an androgen or SARM, and, optionally, (iii) a progestin or SPRM. In a typical therapeutic regimen, this pharmaceutical formulation is administered to the woman at least once daily (e.g., orally, or delivered by transdermal or depot methods) for at least 30 days, at the dosages listed above. Usually, the woman will be treated over the course of several months or years, or even life-long to relieve her of the signs and symptoms resulting from natural or induced impairment of ovarian function.

Alternatively, the woman can be treated with

a pharmaceutical formulation containing each of (i) a SERM and (ii) an estrogen, and, optionally, (iii) a progestin or SPRM. In a typical therapeutic regimen, this pharmaceutical (e.g., orally or delivered by transdermal or depot methods) formulation is administered to the woman at least once daily for at least 30 days at the dosages listed above. Usually, the woman will be treated over the course of several months or years, or even life-long to relieve her of the signs and symptoms resulting from natural or induced impairment of ovarian function.

In still an alternative method, the woman can be treated with a pharmaceutical formulation containing each of (i) a SERM, (ii) an estrogen, (iii) an androgen or SARM, and, optionally, (iv) a progestin or SPRM. In a typical therapeutic regimen, this pharmaceutical formulation is administered to the woman at least once daily for at least 30 days at the dosages listed above. Usually, the woman will be treated over the course of several months or years, or even life-long to relieve her of the signs and symptoms resulting from natural or induced impairment of ovarian function.

In all of the above methods, where the progestin is given, it can be given continuously or cyclicly (i.e., by administering it on only some of the days that the other drugs are administered).

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) to the woman. Typically, the pharmaceutical

formulation will be administered to the woman by applying to the skin of the woman a transdermal patch containing the pharmaceutical formulation, and leaving the patch in contact with her skin (generally for 1 to 5 hours per patch). In another typical method, an intravaginal ring containing the pharmaceutical formulation is inserted into the woman and left in place for 1 to 90 days (e.g., 15 to 30 days) per intravaginal ring. Other transdermal and intravaginal routes of administration (e.g., through use of a topically applied cream, ointment, suppository, and the like) can be used by applying conventional techniques. The pharmaceutical formulations can also be administered via other conventional routes (e.g., oral, subcutaneous, intraperitoneal, intrauterine, sublingual, or intramuscular routes) by using standard methods. In addition, the pharmaceutical formulations can be administered to the woman via injectable depot routes of administration such as by using 1, 3, or 6-month depot injectable or biodegradable materials and methods.

## Other Embodiments

It is to be understood that, while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A pharmaceutical formulation for treating a postmenopausal or perimenopausal woman, comprising:

(i) an estrogen or a selective estrogen receptor modulator (SERM),

(ii) an androgen or a selective androgen receptor modulator (SARM), and

(iii) a progestin or a selective progestin receptor modulator (SPRM) in a pharmaceutically acceptable carrier.

2. A transdermal patch comprising the pharmaceutical formulation of claim 1.

3. An intravaginal ring comprising the pharmaceutical formulation of claim 1.

4. A depot injectable vehicle comprising the pharmaceutical formulation of claim 1.

5. The pharmaceutical formulation of claim 1, wherein the estrogen is selected from the group consisting of conjugated estrogens, esterified estrogens, estradiol valerate, estradiol benzoate, 17-β estradiol, estradiol cypionate, estrone, piperazine estrone sulfate, estriol, ethyl estradiol, polyestradiol phosphate, estrone potassium sulfate, benzestrol, chlorotrianisene, methallenestril, dienestrol, diethylstilbestrol diphosphate, mestranol, diethylstilbestrol, quinestranol, phytoestrogens, animal-derived estrogens, and metabolic derivatives of animal-

derived estrogens.

6. The pharmaceutical formulation of claim 1, wherein the androgen is selected from the group consisting of testosterone, methyltestosterone, fluoxymesterone, testosterone cypionate, testosterone enanthate, testosterone propionate, oxymetholone, ethylestrenol, oxandrolone, nandrolone phenpropionate, nandrolone decanoate, stanozolol, dromostanolone propionate, androstenedione, dehydropepiandrosterone, DHEAS, dihydrotestosterone, testosterone buccilate phytoandrogens, animal-derived androgens, and metabolic derivatives of animal-derived androgens.

7. The pharmaceutical formulation of claim 1, wherein the progestin is selected from the group consisting of progesterone, 17-hydroxy progesterone derivatives, 19-nor testosterone derivatives, 19-nor-progesterone derivatives, norethindrone, norethindrone acetate, norethynodrel, norgestrel, norgestimate, ethynodiol diacetate, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone levo-norgestrel, dl-norgestrel, cyproterone acetate, gestodene, desogestrol, phytoprogestins, dydrogesterone, ethynodiol diacetate, medroxyprogesterone acetate, megestrol acetate, animal-derived progestins, and metabolic derivatives of animal-derived progestins.

8. The pharmaceutical formulation of claim 1, wherein the SERM is selected from the group consisting of tamoxifen, raloxifene, clomiphene, droloxifene, idoxifene, toremifene, tibolone, ICI 182,780, ICI 164,384, diethylstilbesterol, genistein, nafoxidine, moxestrol, 19-nor-progesterone derivatives, and 19-nor-testosterone derivatives.

9. The pharmaceutical formulation of claim 1, wherein the SARM is selected from the group consisting of cyproterone acetate, hydroxyflutamide, bicalutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g]quinolinone derivatives, 1,2-dihydropyridono[5,6-g]quinoline derivatives, and piperidino[3,2-g]quinolinone derivatives.

10. The pharmaceutical formulation of claim 1, wherein the SPRM is selected from the group consisting of RU486, CDB2914, 19-nor-progesterone derivatives, 19-nor-testosterone derivatives, 6-aryl-1,2-dihydro-2,2,4-trimethylquinoline derivatives, 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]quinoline derivatives, 5-alkyl 1,2-dihydrochomeno[3,4-f]quinoline derivatives, and 6-thiophenehydroquinoline derivatives.

11. A hormone replacement method for treating a postmenopausal or perimenopausal woman, the method comprising administering to a postmenopausal or perimenopausal woman a

therapeutically effective amount of the pharmaceutical formulation of claim 1.

12. The method of claim 11, further comprising identifying the woman as being in need of hormone replacement therapy prior to administering the pharmaceutical formulation to the woman.

13. The method of claim 11, wherein the hormone replacement method comprises administering the pharmaceutical formulation to the woman at least once daily for at least 30 days.

14. The method of claim 11, wherein the hormone replacement method comprises administering the pharmaceutical formulation to the woman at least once daily for at least 13 days, followed by administering each of (i) an estrogen or SERM and (ii) an androgen or SARM at least once daily for at least 14 days.

15. The method of claim 11, wherein the pharmaceutical formulation is administered to the woman in a depot injectable vehicle.

16. The method of claim 11, wherein the pharmaceutical formulation is administered to the woman via at least one route selected from the group consisting of transdermal, intravaginal, oral, subcutaneous, buccal, depot injectable, aural, ocular, intranasal, intraperitoneal, intrauterine, sublingual, and intramuscular routes.

17. The method of claim 11, wherein the estrogen in the pharmaceutical formulation is administered at a dosage of 0.01 μg/kg to 4 mg/kg of the body weight of the woman per day.

18. The method of claim 11, wherein the androgen in the pharmaceutical formulation is administered at a dosage of 0.01 μg/kg to 5 mg/kg of the body weight of the woman per day.

19. The method of claim 11, wherein the progestin in the pharmaceutical formulation is administered at a dosage of 0.02 mg/kg to 200 mg/kg of the body weight of the woman per day.

20. The method of claim 11, wherein the SERM in the pharmaceutical formulation is administered at a dosage of 0.01 μg/kg to 100 mg/kg of the body weight of the woman per day.

21. The method of claim 11, wherein the SARM in the pharmaceutical formulation is administered at a dosage of 0.01 μg/kg to 100 mg/kg of the body weight of the woman per day.

22. The method of claim 11, wherein the SPRM in the pharmaceutical formulation is administered at a dosage of 0.01 μg/kg to 100 mg/kg of the body weight of the woman per day.

23. A pharmaceutical formulation for treating a postmenopausal or perimenopausal woman, comprising (i) a SERM and (ii) an androgen or SARM in a pharmaceutically acceptable carrier.

24. A transdermal patch comprising the pharmaceutical formulation of claim 23.

25. An intravaginal ring comprising the pharmaceutical formulation of claim 23.

26. A depot injectable vehicle comprising the pharmaceutical formulation of claim 23.

27. The pharmaceutical formulation of claim 23, further comprising a progestin or a SPRM.

28. A hormone replacement method for treating a postmenopausal or perimenopausal woman, the method comprising administering to a postmenopausal or perimenopausal woman a therapeutically effective amount of the pharmaceutical formulation of claim 23.

29. The method of claim 28, wherein the pharmaceutical formulation further comprises a progestin or a SPRM.

30. A pharmaceutical formulation for treating a postmenopausal or perimenopausal woman, comprising (i) a SERM, (ii) an estrogen, and (iii)

an androgen or a SARM in a pharmaceutically acceptable carrier.

31. A transdermal patch comprising the pharmaceutical formulation of claim 30.

32. An intravaginal ring comprising the pharmaceutical formulation of claim 30.

33. A depot injectable vehicle comprising the pharmaceutical formulation of claim 30.

34. The pharmaceutical formulation of claim 30, further comprising a progestin or a SPRM.

35. A hormone replacement method for treating a postmenopausal or perimenopausal woman, the method comprising administering to a postmenopausal or perimenopausal woman a therapeutically effective amount of the pharmaceutical formulation of claim 30.

36. The method of claim 35, wherein the pharmaceutical formulation further comprises a therapeutically effective amount of a progestin or a SPRM.

37. A pharmaceutical formulation for treating a postmenopausal or perimenopausal woman, comprising a SERM and an estrogen in a pharmaceutically acceptable carrier.

38. A transdermal patch comprising the pharmaceutical formulation of claim 37.

39. An intravaginal ring comprising the pharmaceutical formulation of claim 37.

40. The pharmaceutical formulation of claim 37, further comprising a progestin or a SPRM.

41. A depot injectable vehicle comprising the pharmaceutical formulation of claim 37.

42. A hormone replacement method for treating a postmenopausal or perimenopausal woman, the method comprising administering to a postmenopausal or perimenopausal woman a therapeutically effective amount of the pharmaceutical formulation of claim 37.

43. The method of claim 42, wherein the pharmaceutical formulation further comprises a progestin or a SPRM.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/40061

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/57
US CL :514/169, 170, 178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/169, 170, 178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CHEMICAL ABSTRACTS

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MED LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US, 5,340,585 A (PIKE et al) 23 August 1994, see entire document. | 1-43 |
| X | US 5,770,226 A (HUGHES et al) 23 June 1998, see entire document. | 1-43 |
| A | US 5,846,960 A (LABRIE et al) 08 December 1998, see entire document. | 1-43 |
| X,P | US 5,955,455 A (LABRIE) 21 September 1999, see entire document. | 1-43 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"E" earlier document published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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